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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,148	04/16/2001	Benjamin F. Cravatt	SCRIP1210-4	8213

7590 08/11/2003

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EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/11/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/836,148	CRAVATT ET AL.	
	Examiner	Art Unit	
	My-Chau T. Tran	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *4 and 7-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, and 5-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 6-8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

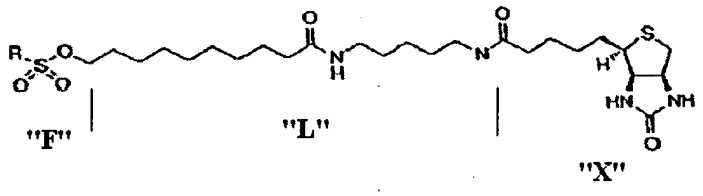
DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (Claims 1-6) in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 7-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. Applicant's species election with traverse in Paper No. 9 is acknowledged. The elected species are follows:



, wherein "R" = phenyl; "F" = sulfonyl; "L" = *N*-(5-pentylamine)-decanamide; and "X" = biotin.

4. Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species (e.g. "R" is pyridyl), there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Drawings

5. The drawings filed on 7/20/01 are acceptable subject to correction of the informalities indicated on the attached "Notice of Draftsperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code such as pg. 42(paragraph [0140]), pg. 67 (paragraph [0204]), and others throughout the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. Claims 1-3 and 5-6 are treated on the merit in this Office Action.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, and 5-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (This is a written description rejection).

The instant claim 1 recite a method for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing a probe wherein the probe has a formula: R(F-L)-X (e.g. X is a ligand, L is a linking group, F is a phosphonate or sulfonyl functional group, and R is bonded to F and a moiety). The method steps comprises: 'a) combining at least one probe with an untreated portion of said mixture and with a portion inactivated with a non-covalent agent under conditions for reaction with said target proteins; b) sequestering proteins conjugated with said at least one probe from each of said mixtures; c) determining the proteins that are sequestered; and d) comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of said candidate compound with said target proteins.

The specification description discloses several methods. In one method on page 34 (paragraph 0119), "*For two samples in which the active proteins of a given family present in these samples are to be quantitatively compared, the following method can be used. A portion of each sample is treated so that the active proteins in the one portion are inactivated. Protein portions of the active and inactive samples are then treated with isotopic variants of the same ABP (e.g., one variant contains 5-10 hydrogens (light probe) and is applied to the inactive portions, the second variant has these 5-10 hydrogens substituted with deuteriums (heavy probe)*

and is applied to the active portions). After sufficient reaction time, the inactive and active portions of each sample are then separated from their respective ABPs (e.g., by gel filtration chromatography), combined to form a mixed sample, and this mixed sample is digested with a protease (e.g., trypsin) to create a mixture of peptides. These peptides are then treated with an affinity support to selectively isolate peptides covalently tagged with an ABP (e.g., avidin is the affinity support if the probe's tag is biotin). The isolated peptides are then optionally separated by a liquid chromatography step (e.g. HPLC) and characterized by mass spectrometry. ABP-tagged peptides representing active proteins are defined as those found in significantly greater excess (e.g., at least three-fold greater in mass ion abundance) bonded to the heavy probe than to the light probe. The molecular sequence of these peptides can be determined by Tandem Mass Spectrometry to provide the identity of the active proteins from which the ABP-labeled peptides are derived. This first procedure will thereby determine the members of a given protein family that are both present and active in the sample. Two protein portions of the active sample are then treated with the heavy and light probes and processed as described above. The levels of active protein activities will be quantitatively compared across the two samples by ratioing the mass ion abundances corresponding to heavy and light probe-bonded versions of individual peptides. Only those peptides that were determined in the first procedure to represent active proteins will be compared in this manner." The specification description and examples are directed to the syntheses of a specific probe (e.g. the for biotinylated fluorophosphonate probe such as FP-biotin and FP-peg-biotin) that have specificity toward an "active target member" (e.g. serine hydrolases) and the method of detecting serine hydrolases using these specific probe (e.g.

the for biotinylated fluorophosphonate probe such as FP-biotin and FP-peg-biotin) in sample such as rat tissue.

The specification clearly does not teach the presently claimed method "*for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing a probe*" when the interaction is between the target proteins and the probe as claimed in steps (a)-(c). The specification clearly does not teach any method for screening ***any*** candidate compound for bioactivity with ***any*** target proteins. The specification clearly did not provide any guidance as to the "relationship" between the candidate compound and the probe. Additionally, the specification and examples clearly do not provide an adequate representation regarding the open ended claimed the "target proteins" (e.g. other type of hydrolases such as glycoside hydrolases or other type of enzymes such as ligases) and the probe specific for other type of "target proteins" for the method of the presently claimed invention.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s) (e.g. all type of protein).

In the present instance, the claimed method contains no identifying characteristics regarding the "active target members" being detected and the probes specific to the "active target members", guidance method "*for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing a probe*" when the interaction is between the target proteins and the probe as claimed in steps (a)-(c), guidance method for screening ***any*** candidate compound for bioactivity with ***any*** target proteins, and any guidance as to the "relationship" between the candidate compound and the probe. Additionally, the narrow scope of examples directed to specific detection of serine hydrolases and the probe specific to serine hydrolases is clearly not representative of the scope of detecting all type of proteins with any type probe specific to the protein of interest of the presently claimed invention. Thus, applicant was not in possession of the claimed method and genus (e.g. the "target proteins", candidate compound, "probe").

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-3 and 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The method step (a) of claim 1 is vague and indefinite because it is confusing as to whether the "condition for reaction" between the probe and target proteins are the same of different in each portion of the mixture (e.g. untreated portion and inactivated with a non-covalent agent).

b) The term "untreated" of claim 1 is a relative term, which renders the claim indefinite. The term "untreated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention (e.g. "untreated" refers to no addition of the "non-covalent agent" or different assay condition).

c) Clarification is needed as to the "inactivated" portion of claim 1 step (a) because it is unclear as to what is being considered "inactivated" in the proteomic mixture (e.g. the target proteins or all the proteins in the mixture). Further the dependent claim 6 defines the "non-covalent agent" is heat, if heat causes the "inactivity" in the proteomic mixture (e.g. "killing" all the cells or causing "precipitation" of all the protein) in what ways is the "comparison" between the "untreated" proteomic mixture and the "treated" proteomic mixture for bioactivity of the candidate compound or the reaction of the "probe" to the target protein.

d) Claim 1 recites the limitation "mixture" in line 16. There is insufficient antecedent basis for this limitation in the claim.

c) Clarification is needed as to the "combining" step (e.g. step (a)) of claim 1 because it is unclear whether the step refers to the "addition" of the probe to each portion of the proteomic mixture or the "combining" of both portions of the proteomic mixture.

d) Clarification is needed as to when F is phosphonate F is also fluorine of claim 1.

e) Claim 1 step (c) is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the addition of the candidate compound to the sample and its reaction with the target proteins. It is unclear as to the correlation between the "bioactivity of the candidate compound with the target proteins" and that of the reaction between the target proteins and the probes.

f) Claims 2 and 3 recite the limitation of "enzymes" in line 2. There is insufficient antecedent basis for this limitation in the claim 1.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-2 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gygi et al. (*Nature Biotechnology*, **1999**, 17(10):994-999) and Liu et al. (*PNAS*, **1999**, 96(26): 14694-14699).

It is interpreted that the "candidate compound" is synonymous to the "probe" in the presently claimed method.

Gygi et al. disclosed a method for quantitative analysis of complex protein mixtures using isotope-coded affinity tags (ICAT) (Abstract; pg. 994, right col., 6-9). The method comprises of the following steps: 1) The side chains of cysteinyl residues in a reduced protein sample representing one cell state are derivatized with the isotopically light form of the ICAT reagent. The equivalent groups in a sample representing a second cell state are derivatized with the isotopically heavy reagent (refers to the combining step). (2) The two samples are combined and enzymatically cleaved to generate peptide fragments (refers to the sequestering step). (3) The tagged peptides are isolated by avidin affinity chromatography (refers to the determining step). (4) Finally, the isolated peptides are separated and analyzed by LC-MS/MS (electrospray ionization (ESI) MS/MS, in conjunction with microcapillary liquid chromatography (LC)) (pg. 994, right col., 12-24; figure 2) (refers to the comparing step).

The method of Gygi et al. does not expressly disclose that the probe is fluorophosphonyl and the target proteins are serine hydrolases.

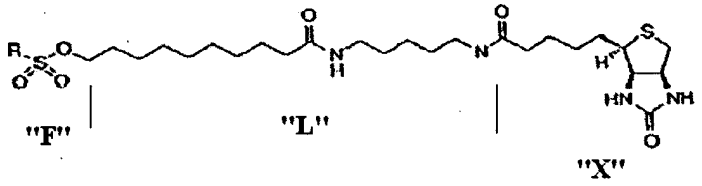
Liu et al. disclosed a method of activity-based protein profiling using an active site directed probe (Abstract). The probe is a biotinylated fluorophosphonate, FP-biotin, (pg. 14694, left col., lines 30-33). The method steps of reacting protein samples (proteomic mixture) with FP-biotin (activity-based probe) include combining FP-biotin mixture with the protein samples

and detecting the FP-biotin-reactive proteins by SDS/PAGE-Western Blotting (pg. 14695, right col., lines 26-64). The FP-biotin-reactive proteins are further analyzed by MALDI mass spectrometry (pg. 14696, left col., lines 11-15). FP-biotin can react with numerous serine hydrolyses (target enzyme) in crude cell and tissue samples (pg. 14698, left col., lines 1-8).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include that the probe is fluorophosphonyl and the target proteins are serine hydrolases as taught by Liu et al. in the method of Gygi et al. One of ordinary skill in the art would have been motivated to include that the probe is fluorophosphonyl and the target proteins are serine hydrolases in the method of Gygi et al. for the advantage of providing a probe that is specific for profiling in a single class of proteins (Liu: pg. 14694, lines 30-33) since both Gygi et al. and Liu et al. disclose method of detecting proteins from a crude cell samples (Gygi: pg. 994, right col., 6-9, and pg. 995, fig. 2; Liu: pg. 14698, left col., lines 1-8).

Allowable Subject Matter

15. The following is a statement of reasons for the indication of allowable subject matter: The elected species of probe with the formula: R(F-L)-X, wherein "R" = phenyl; "F" = sulfonyl; "L" = *N*-(5-pentylamine)-decanamide; and "X" = biotin. The claimed structure is



The structure of the presently claimed elected species of probe is not taught or suggested by the closest prior art of Liu et al. (*PNAS*, **1999**, 96(26): 14694-14699).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 703-305-6999. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 703-306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

mct
August 7, 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER